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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,504	11/19/2001	Michael E. Himmel	NREL 99-38	3921

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,504	HIMMEL ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 26-31* is/are pending in the application.

4a) Of the above claim(s) *1,2,9-21 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5,6,8 and 29-31* is/are rejected.

7)☒ Claim(s) *4 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21, 26 through 31 are still at issue and are present for examination. Claims 3-8 and 29-31 are now under consideration. Claims 1-2, 9-21, 26-28 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 12-1-03, 1-30-04 and 5-24-04 have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn all previous rejections under 35 U.S.C. 112, 2nd paragraph in view of claim amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 and claims 30 and 31 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 recites the phrase "or a structural analog thereof". The metes and bounds of the above phrase are not clear to the Examiner. It is not clear as to what would be the function of the structural analog i.e., whether the structural analog would continue to have endoglucanase activity or not.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5, 8, 29-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the specific activity of EI endoglucanase isolated from *Acidothermus cellulolyticus* on pretreated biomass, comprising the replacement of the specific active site associated glycosyl stabilizing amino acid, Y at position 245 with G or Y at position 42 with R or W at position 82 with R as represented in the respective amino acid sequences SEQ ID NO:10, 12, 14, does not reasonably provide enablement for a method of increasing the specific activity of any glycosyl hydrolase enzyme isolated from any or all sources acting on any or all type of substrates, comprising the replacement of any active site associated glycosyl stabilizing amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 3-5, 8, 29-30 are so broad as to encompass a method of increasing the specific activity of any glycosyl hydrolase enzyme isolated from any or all sources acting on any or all type of substrates, comprising the replacement of any active site associated glycosyl stabilizing amino acid. The scope of the claims is not commensurate with the enablement

provided by the disclosure with regard to the application of a single method for an extremely large number of glycosyl hydrolases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the single EI endoglucanase isolated from *A.cellulolyticus* and comprising the amino acid sequence as depicted in Example 7 of the specification. It would require undue experimentation of the skilled artisan to make and use the claimed method to increase the specific activity of any or all glycosyl hydrolases including structural analogs of endoglucanases. The specification is limited to a method of enhancing the specific activity of a single EI endoglucanase against a single substrate, i.e., pretreated biomass, but provides no guidance with regard to using the same method on any glycosylhydrolase isolated from any source and having any structure. In view of the great breadth of the claim, amount of experimentation required to use the above method on any glycosyl hydrolase which includes a large number of different hydrolytic enzymes acting on a wide range of substrates, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue

experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the method encompassed by these claims.

While recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses a method of increasing the specific activity of any glycosyl hydrolase enzyme isolated from any or all sources acting on any or all type of substrates, comprising the replacement of any active site associated glycosyl stabilizing amino acid because the specification does not establish that: (A)the method works in all or any glycosyl hydrolases which includes a large number of different enzymes; (B) the specific activity of the glycosyl hydrolases is enhanced irrespective of the type of substrate; (C) a rational and predictable scheme for identifying and modifying any active site residue in any glycosyl hydrolase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any glycosyl hydrolase and all or any type of substrates. The

scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a method that applies to all types of glycosyl hydrolases and all types of substrates is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicant has traversed the above rejection arguing that, "...The Office notes that Applicants have shown an improvement in activity by replacing tyrosine at position 245 in glycohydrolase from *A. cellulolyticus*. but have not provided knowledge or guidance as to how this might be done outside the limited scope of the enabled species" and that "Such knowledge may be found by way of examples in paragraph (0025) of the published Application and in the table there following, which shows analogous substitution sites in glycosyl hydrolase family enzymes". While Examiner agrees that applicant has support for such specific examples and is enabled for those specific analogous, he respectfully disagrees that such guidance is enough for claiming a method of increasing the specific activity of the entire group of glycosylhydrolases. It must be remembered that the family of glycosylhydrolases includes a variety of hydrolases which have separate class of substrates and results in generation of a variety of products. The examples provided by the applicant is specific for endoglucanases only but all members of glycosyl family.
Applicant also argues that "the referenced page provides, by way of examples a rationale or theory for making such substitutions in a genus as have been shown to work in the illustrated species and that additional proof that applicant s were in possession of the theory leading to effective modifications of the enzyme at the time of filing may be found in kinetics discussion of

paragraph 0058. Again while applicants may have provided a theory or a rationale for making amino acid changes they have not unequivocally show that said rationale would be effective on every member of glycosylhydrolase family. As rightly pointed out by the applicant, the determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of invention and the state of state of art" and that is what examiner has exactly done here. It can be concluded, at the most, applicant has provided support for a method of increasing the specific activity of "endoglucanases" but not a method for increasing the specific activity of all members of the complex group of enzymes included in the large family, "glycosyl hydrolases". As stated earlier, applicant's arguments are not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing method of increasing the specific activity of all members of glycosyl hydrolases as claimed by applicants requires that one of ordinary skill in the art know or be provided with a universal method for the selection of specific amino acid residues in each and every member of the glycosyl hydrolase family. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. Hence the above rejection is maintained. Examiner agrees with the applicant that

claims 4 and 7 are more specific and therefore has not included them in the above rejection. However, the rejection is maintained with respect to the remaining claims as listed above.

Claims 3-5 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3-5 and 8 are directed to a method of enhancing the specific activity of any glycosyl hydrolase. Claims 3-5 and 8 are rejected under this section of 35 USC 112 because the claims are directed to a method of using a genus of polypeptides that have not been disclosed in the specification. No description has been provided of the polypeptide sequences encompassed by the claim. No information, beyond the characterization of a single specific polypeptide having EI-endoglucanase activity and isolated from *A.cellulolyticus* (in Example 7) has been provided by applicants which would indicate that they had possession of the claimed genus of polypeptides. The specification does not contain any disclosure of the structure of the polypeptide sequences within the scope of the genus to be used in the claimed method. The genus of polypeptides is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses a method for only a single species of the genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the genus for use in the claimed method. Therefore, one skilled in the art cannot

reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicant has not specifically addressed the above rejection. However, said rejection is maintained by the Examiner.

Claims 29-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 29-31 are directed to a method of enhancing the specific activity of an EI endoglucanase or structural analog thereof. Claims 29-31 are rejected under this section of 35 USC 112 because the claims are directed to a method of using a genus of polypeptides that have not been disclosed in the specification. No description has been provided of the polypeptide sequences encompassed by the claim. No information, beyond the characterization of a single specific polypeptide having EI-endoglucanase activity and isolated from *A.cellulolyticus* (in Example 7) has been provided by applicants which would indicate that they had possession of the claimed genus of polypeptides. The specification does not contain any disclosure of the function of the polypeptide sequences (structural analogs) within the scope of the genus to be used in the claimed method. The genus of polypeptides is a large variable genus including

peptides which can have a wide variety of function. Therefore many functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses a method for only a single species of the genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the genus for use in the claimed method. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Conclusion

Claims 4 and 7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

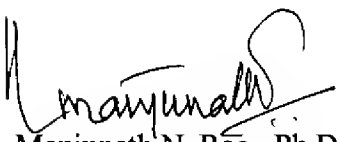
None of the other claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Manjunath N. Rao. Ph.D.
August 10, 2004